The effect of neutrophil lymphocyte ratio and monocyte HDL ratio in indicating additional arterial disease in patients scheduled to undergo elective coronary bypass operation

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Original Article

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ABSTRACT

Objective: We aimed to investigate the role of neutrophil / lymphocyte ratio (NLR) and monocyte / HDL ratio (MHR) in routine blood tests before surgery in predicting the presence of carotid artery and peripheral artery disease in patients scheduled for Coronary artery bypass graft(CABG)

Design: Retrospective study

Setting: Department of Cardiovascular Surgery, University of Health Sciences, Mehmet Akif İnan Training and Research Hospital

Subjects: A total of 354 consecutive patients who scheduled to undergo elective CABG Operation

Intervention: Predictive values of the variables were measured for the atherosclerosis extensity.

Main outcome measure(s): The relationship between preoperative NLR –MHR and concomitant arterial disease in patients scheduled to undergo CABG.

Results: A total number of 310 patients in the Group 1 (without additional arterial disease) (64.5% male, mean age: 59.1 ± 8.7 years) and 44 patients in the Group 2 (with additional arterial disease) (72.7% male, mean age: 65.5 ± 12.3 years) were recorded in the study. There were statistically difference between two groups in terms of age (p = 0.003), presence of Diabetes mellitus (p = 0.032). In multivariate analysis; advanced age, NLR and MHR were identified as an independent predictor of concomitant arterial disease. In ROC curve analysis, for NLR it was determined a cut-off level of 2.85 for predicting concomitant arterial disease (96% sensitivity and 46% specificity), for MHR it was determined a cut-off level of 8.65 (90% sensitivity and 42% specificity).

Conclusion: In this study, we found that simple blood tests may shed light on the detection of additional arterial diseases in patients planned to undergo CABG.

KEY WORDS: Coronary artery disease, Peripheral artery disease, Carotid artery disease, Neutrophil to lymphocyte ratio, Monocyte to HDL ratio

INTRODUCTION

Nowadays, the diagnosis of atherosclerotic cardiovascular diseases is more frequent with prolonged survival and progressive technology. Coronary artery disease (CAD) is one of the most frequent disease of atherosclerotic cardiovascular diseases. The gold standard treatment method is coronary artery bypass graft (CABG) when coronary artery disease presents as mutipl vessel disease.[1] Coronary artery disease may be accompanied by other system arteriopathies such as peripheral arterial disease (PAD) and carotid artery stenosis (CAS). In patients scheduled for coronary artery bypass surgery, CAS with 50% and more stenosis can be seen in 30% of the patients.[2] Only carotid artery disease is even important because of possible cerebrovascular risks.[3] This situation is not a cause of cerebrovascular disease alone, but it is an important risk factor. Therefore, it is important to make a diagnosis before CABG operation. Preoperative recognition of peripheral artery disease in patients undergoing CABG is also important. Possible iliac artery stenoses can lead to serious complications during and after surgery.[4]

Studies have shown that various biomarkers can demonstrate the presence and severity of atherosclerosis. In these studies, some parameters that increased in blood were related to atherosclerotic cardiovascular diseases.[5, 6]

In our study, we aimed to investigate the predictive value of neutrophil / lymphocyte ratio (NLR) and monocyte / HDL ratio (MHR), that can be obtained from routine blood tests before surgery, on the presence of carotid artery and/or peripheral artery disease in patients who scheduled to undergo CABG.

MATERIAL AND METHODS

The patients who were hospitalized with CABG between December 2014 and December 2018 were included in the study. The study was approved by the Ethical Committee of Sanlıurfa Harran University Faculty of Medicine. The study was conducted in accordance with the principles of the Declaration of Helsinki. The data of the patients were retrospectively obtained from hospital data system and archive records. Patients undergoing emergency operations, patients with known systemic inflammatory disease, new myocardial infarction, patients with additional cardiac surgery (aneurysm, valvular heart diseases etc.) except for coronary artery disease were excluded from the study. After applying these exclusion criteria, 354 consecutive patients were included in the study.

According to the tests and physical examination data, patients who didn't have any additional artery disease except for coronary artery disease were included in Group 1. Patients having 50% or more stenosis in carotid or peripheral arteries were classified as Group 2. Demographic characteristics (age, sex, hypertension, etc.) and preoperative blood tests of all patients were recorded (hemogram, urea, creatinine, etc.).

Diagnosis of additional artery disease

Carotid Doppler ultrasonography is performed in all patients routinely in our clinic in the preoperative preparation of coronary bypass operations. Thus, the patients can be diagnosed with a possible stenosis and occlusion. The diagnosis of peripheral arterial disease was made by doppler ultrasonography (in 30 patients), conventional angiography (in 5 patients) and / or computed tomographic angiography (in 9 patients) in patients with pathology on physical examinations. According to these results, patients who had 50% or more stenosis in the peripheral and / or carotid artery system were evaluated as patients with additional artery disease.

Laboratory measurements

Preprandial blood samples were obtained from an antecubital vein of every patient when the patients entered to our clinic. The tubes with EDTA were utilized for automatic blood count with reference to the procedures of our hospital. An automated hematological analyzer was used for measuring hematologic parameters (Coulter LH 780 Analyzer, CA, USA). Furthermore, NLR and MHR were assessed.

Statistical analysis

SPSS 21.0 (IBM Statistical Package for the Social Sciences Statistic Inc. version 21.0, Chicago, IL, USA) was utilized for analysis. Descriptive statistics such as mean and standard devations were calculated for continuous and ordinal variables. The frequencies and percentages of mominal variables were analyzed. In exploring the normality of the data, “Kolmogorov-Smirnov test and Shapiro-Wilk tests” were performed. For comparing two groups, “Student’s t test and Mann-Whitney U test” were used for continuous variables with and without normal distribution respectively. Nominal variables were compared via “Chi Square test”. Predictors of other system arterial disease were defined via binary logistic regression analysis. P value that was lower than 0.05 was determined as statistically significant. “Receiver-operating characteristic (ROC) curve” was applied for the prediction of other system arterial disease and “the area under the curve (AUC)” was calculated for NLR and MHR.

RESULTS

A total number of 310 patients in the Group 1 (64.5% male, mean age: 59.1 ± 8.7 years) and 44 patients in the Group 2 (72.7% male, mean age: 65.5 ± 12.3 years) were recorded in the study. There were statistically difference between two groups in terms of age (p = 0.003) and presence of Diabetes mellitus (DM) (p = 0.032). However, there was no statistically difference between two groups in terms of gender, percutaneous coronary intervention history, hypertension(HT), smoking and ejection fraction(EF). The demographic and clinical features of the patients were shown in Table 1.

The comparison of laboratory measurements between two groups were shown in Table 2. Both Group 1 and Group 2 were similar to each other in regard to laboratory findings. Additionally, there were statistically significant difference between two group in terms of monocyte count (p <0.001), NLR (p = 0.001) and MHR (p < 0.001) (Table2).

Factors related to determine concomitant arterial disease in patients scheduled for CABG were included univariate logistic regression analysis. In unadjusted univariate logistic regression analysis, the presence of extracardiac arterial disease was significantly correlated with advanced age (OR [odds ratio]: 1.076, 95% CI [confidence interval]: 1.024-1.131, p = 0.004), DM (OR: 0.376, 95% CI: 0.150-0.941, p = 0.037), NLR (OR: 1.434, 95% CI: 1.074-1.914, p = 0.015) and MHR (OR: 3.099, 95% CI: 1.674-5.736, p <0.001), but was not correlated with gender and target vessel. In multivariate analysis; advanced age, NLR and MHR were identified as an independent predictor of concomitant arterial disease. (OR: 1.052, 95% CI: 1.002-1.105, p = 0.042; OR: 1.500, 95% CI: 1.036-2.171, p = 0.032; OR: 3.004, 95% CI: 1.540-5.860, p = 0.001,respectively) (Table 3).

In ROC curve analysis, for NLR it was determined a cut-off level of 2.85 for predicting concomitant arterial disease (AUC: 0.722, 95% CI: 0.638-0.806, log rank p = 0.001, 96% sensitivity and 46% specificity), for MHR it was determined a cut-off level of 8.65 for predicting concomitant arterial disease (AUC: 0.791, 95% CI: 0.703-0.879, log rank p < 0.001, 90% sensitivity and 42% specificity) (Figure 1).

DISCUSSION

Atherosclerosis is a condition arising out of chronic vascular inflammation. As a result of this inflammation, inflamed cytokines and chemokines penetrate into the inflamed vascular endothelium.[7] The atherosclerotic process progresses within a certain relationship with the entire cardiovascular system.[8] The clinical outcomes of this condition are generally seen as CAD, PAD and CAS. These diseases can be detected separately in the same person or can be seen together. The possible PAD and / or CAS cases should be recognized in the preoperative period, especially in patients undergoing CABG.

Neutrophils in circulation lead to the progression of atherosclerosis by clinging to the damaged vascular endothelial regions. Thus, chemokines come into the region, proliferation develops and atherosclerosis progresses and the vessel wall narrows.[9] Monocyte activation also plays a role in the atherosclerotic process by modulating inflammatory cytokines. By attaching to damaged endothelial sites, monocytes aggregate the inflammatory process and play a role in thrombotic events.[10] By contrast with, HDL takes a preventive role in the progression of the atherosclerotic process.[11]

In recent years, the relationship between blood parameters and cardiovascular system diseases has been the subject of interest and various studies have been carried out on this topic. In addition to the diagnostic importance, the prognostic values of these parameters after cardiovascular operations were also investigated. Aykan *et al* investigated the role of NLR in investigating the severity of peripheral artery disease. In this study, patients were divided into two groups as TASC (Transatlantic Intersociety Consensus) -A-B and TASC-C-D and NLR was significantly higher in TASC-C-D group. In the Roc analysis, the cut-off of NLR was determined as 3.05 (sensitivity = 75.0%, specificity = 62.9%, AUC = 0.678, 95% CI = 0.688 (0.784, p <0.001).[12]

The prognostic significance of NLR in patients undergoing CABG was investigated by Ay *et al*. and the patients were divided into two groups as below 45 years of age and above. Mortality and NLR were found to be significantly higher in the elder patient group and it was stated that NLR may be a predictor of mortality in this study.[13] Arbel and his colleagues investigated the role of NLR in determining the severity of coronary artery disease by evaluating consecutive 3005 patients who had coronary anjiography. They classified the patients into 3 groups by their NLR. The first group (30% of patients) consisted of patients whose NLR were below 2, the second one (30% of patients) comprised of patients whose NLR were between 2 and 3 and the last one (40% of patients) included patients whose NLR were upper than 3. They found a significant difference in CAD severity among these 3 groups (p<0.001). They also found a positive correlation between higher NLR and CAD severity (p<0.001). At the same time, close relationship with adverse events was detected at 3-year follow-up.[14]

Similarly, MHR was investigated in cardiovascular system diseases. The clinical significance of MHR was evaluated by Cetin *et al* on the 2661 patients with acute coronary syndrome. They determined that MHR showed the severity of coronary artery disease. In this study, the mean follow-up period was 31.6 months, and the relationship between increased MHR and major adverse cardiovascular events was determined.[15] Tekkesin *et al* investigated the effects of MHR on atrial fibrillation in patients undergoing

CABG. In this study, preoperative MHR values were significantly higher in patients with atrial fibrillation in the postoperative period.[16]

In our study, we aimed to investigate the predictive value of MHR and NLR in addition to the presence of CAS and PAD in patients scheduled for CABG. We divided patients into two groups as patients with CAS or PAD and patients without additional artery disease. As a result of our study, we determined that these parameters obtained from preoperative routine blood tests of the patients may guide us. Although MHR and NLR values have good sensitivity, their overall specificity is poor (42% and 46%).

Preoperative preparation of coronary bypass operations is as valuable and important as the surgical technique stage of the operation. In these patient groups, possible lung diseases, uncontrolled diabetes and other systemic diseases may overshadow our technical surgical success. Carotid artery disease and PAD should be detected in the preoperative period and essential precautions should be taken. In particular, In patients with the possible iliac artery stenosis, it may be difficult to apply to intra-aortic balloon pump, a very valuable device in the weaning of cardiopulmonary bypass. In this case, it may be necessary to perform more complicated methods than the femoral approach.[17] In addition, it is very important to diagnose the potential severe CAS at preoperative stage. We may need to make changes in our operation strategies in this clinical situation. In this case, the operation method is determined by considering the clinical evaluation of CAD and CAS.[18]

CONCLUSION

In this study, we found that simple blood tests may shed light on the detection of additional arterial diseases in patients planned to undergo CABG. Misdiagnosing possible severe PAD or CAS disease may lead to catastrophic outcomes in CABG operations which are a major surgery. According to our study, NLR and MHR can cause us to suspect for additional arterial diseases.

Limitations

This study is a retrospective study carried out in homogeneous groups of patients. A smaller number of patients is also the limiting factor of the study. In addition, group 2 had a smaller number of patients (44 patients).

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Declaration of authorship: The author has directly participated in the planning, execution, analysis or reporting of this research paper. The author has read and approved the final version of the manuscript.

Conflict of interest: None

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Table 1: Demographic data of the patients

Paremeters	**Group 1 (n=310)**	**Group 2 (n=44)**	***P* value**
Age(years) (mean±sd)	59.1±8.7	65.5±12.3	**0.003**
Male/Female gender, n	200/110	32/12	0.448
Previous PCI, n(%)	88(28.3%)	18(40.9%)	0.230
Target vessel n, (mean±sd)	2.9±1.01	3.41±1	0.073
COPD, n(%)	64(20.6%)	8(18.1%)	0.786
Hypertension, n (%)	206 (66.4%)	28 (63.6%)	0.794
Diabetes mellitus, n (%)	74 (23.8%)	20 (45.4%)	**0.032**
BMI (kg/m^2)	28.7±4.2	27.6±3.9	0.156
Smoking, n (%)	114(36.7%)	20 (45.4%)	0.432
Ejection fraction (%)(mean±sd)	51.7±7.3	50.9±6.7	0.236

PCI: Percutaneus coronary intervention, COPD: Chronic obstructive pulmonary disease, BMI: Body mass index

Table 2: Laboratory variables of the patients

Parameters	**Group 1 (n=310) (mean ± SD)**	**Group 2 (n=44) (mean ± SD)**	***P* value**
Hematocrit (%)	38.9±5.1	37.1±5.9	0.483
White blood Cell (10^3/µL)	8.9±2.9	9.6±3.1	0.339
Platelet (10^3/µL)	279.3±73.2	288.7±69.2	0.354
RDW(%)	13.7±1.4	14.4±1.3	0.249
MPV(fL)	8.5±1.2	8.8±1.3	0.543
Neutrophil (10^3 mL)	6.4±1.2	6.9±1.1	0.364
Lymphocyte(10^3 mL)	2.9±1.4	2.2±1.2	0.456
Monocyte (10^9 L)	370.7±122.8	398.2±133.2	**<0.001**
BUN (mg/dL)	17.9±6.7	19.8±9.7	0.124
Creatinine (mg/dL)	1.1±0.5	0.9±0.5	0.486
C Reactive protein (mg/dL)	7.8±11.3	10.1±12.6	0.146
Total Cholesterol (mg/dL)	191.0±68.5	199.8±53.7	0.351
LDL-C (mg/dL)	126.8±43.7	129.2±38.1	0.256
HDL-C (mg/dL)	44.1±6.9	41.7±9.2	0.066
TG (mg/dL)	184.8±89.6	195.3±67.5	0.453
NLR	3.3±1.3	4.1±1.1	**0.001**
MHR	7.9±1.5	9.4±0.7	**<0.001**

RDW: Red cell distribution width, MPV: Mean platelet volume, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride, NLR: Neutrophil to lymphocyte ratio, MHR: Monocyte to HDL ratio

Table 3: Logistic regression analysis for predictors to identify other system arterial disease

	Univariate analysis				Multivariate analysis		
Variables	***P***	**Exp(B) Odds Ratio**	**95% C.I. Lower Upper**		***P***	**Exp(B) Odds Ratio**	**95% C.I. Lower Upper**
Age	**0.004**	1.076	1.024-1.131		**0.042**	1.052	1.002 - 1.105
Male gender	0.450	1.467	0.543-3.964		--	--	--
Target vessel	0.075	1.526	0.958-2.430		0.144	1.552	0.860 - 2.802
DM	**0.037**	0.376	0.150-941		0.057	.731	1.111 - 1.284
Previous PCI	0.226	1.356	0.654-2.826		--	--	--
NLR	**0.015**	1.434	1.074-1.914		**0.032**	1.500	1.036 - 2.171
MHR	**<0.001**	3.099	1.674-5.736		**0.001**	3.004	1.540 -5.860

DM: Diabetes mellitius, PCI: Percutaneus coronary intervention, NLR: Neutrophil to lymphocyte ratio, MHR: Monocyte to HDL ratio

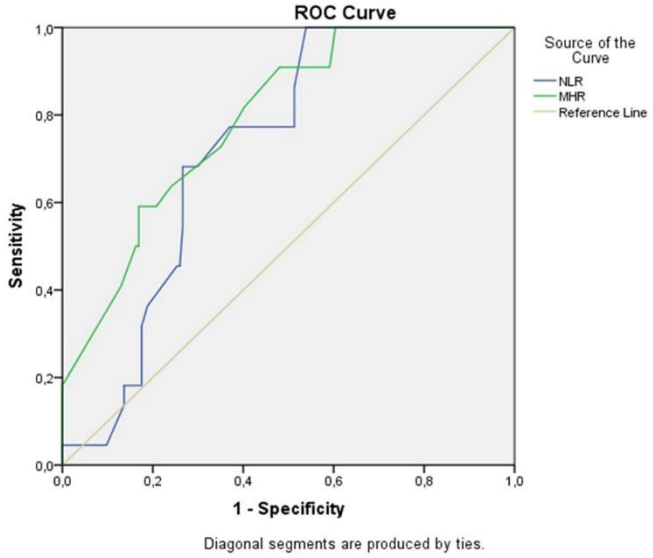

Figure 1: Receiver operation characteristic (ROC) curve and area under the curve (AUC) for Neutrophil to lymphocyte ratio(NLR) levels and monocyte to HDL ratio(MHR) levels for predicting to identify concomitant carotid artery disease and peripheral artery disease(PAH). (NLR: cut-off=2.85, 96% sensitivite, 46% spesifite, MHR: cut-off= 8.65, 90% sensivite, 42% spesifite)